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(54) Title: ANTI-INFLAMMATORY LINIMENT

(57) Abstract

A composition for topical application to the skin adjacent a locus of inflammation includes an oil, being linseed oil or a substantially equivalent oil thereto, or an effective amount of a component thereof, as the primary pain relieving agent. The composition also includes a thinner or solvent therefor which assists in moving the said agent through the skin to said locus. The thinner may have a synergistic effect on the activity of the agent. A method for the relief of inflammation by using the aforementioned composition is also provided.

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ANTI-INFLAMMATORY LINIMENT

FIELD OF INVENTION

The present invention relates to compositions for topical application for the relief of pain, in particular pain arising from inflammation of the joints, such as arthritic pain, and pain arising from headaches, such as migraine.

BACKGROUND ART

Pain arising from inflammation, particularly in the joints, in mammals, particularly humans, arises for a wide variety of reasons including over-exercising of the joints, physical injury, rheumatism and arthritis. A number of parenteral and topical compositions exist which are alleged to either cure or relieve the pain arising out of these causes of inflammation.

For example, aspirin is a commonly used anti-inflammatory drug, taken orally for the relief of pain. Cortisone and its analogs is also considered to be an anti-inflammatory drug and may be used both in parenterally administered or topically administered formulations. In particular cortisone has several undesirable side effects which limit its application.

There also exist a number of pain relieving creams for topical applications to the joint. However, these usually provide only temporary alleviation of the pain.

DISCLOSURE OF INVENTION

The present invention results from a discovery by the present inventors that a composition containing linseed oil when applied topically to an inflamed region reduced the inflammation and pain resulting therefrom. It was also discovered that the linseed oil had to be dispersed in an appropriate solvent or thinner medium for the anti-inflammatory and analgesic affects of the composition to be noted. Some of the preferred thinners clearly displayed a synergistic effect on the activity of the linseed oil.

According to the invention, there is provided a composition for topical application to the skin adjacent a locus of inflammation, said composition comprising an oil, being linseed oil or a substantially equivalent oil thereto, or an effective amount of a component thereof, and a thinner therefor which assists in moving said oil or component through the skin to said locus.

According to another embodiment of the invention, there is provided a method for the relief of inflammation, particularly of the joints, said method comprising topically applying to the skin adjacent a locus of inflammation a composition comprising an oil being linseed oil, or a substantially equivalent oil thereto or an effective amount of a component thereof, dissolved in a thinner therefor, which thinner assists in moving said oil or component thereof through the skin to the locus.

Preferably the composition of the present invention comprises about 80% by volume of linseed oil and the remaining % by volume thinner. The composition may also contain an antioxident, such as wheatgerm oil or Vitamin E to increase its shelf life.

In tests described later in the specification, compositions which comprise linseed oil and a thinner, the thinner being preferably selected from one or more members of the group comprising mineral or distilled turpentine, methyl, ethyl and isopropyl salicylate esters, eucalyptol (also known as cineole), tea tree oil (also known as ateol) and oil of wintergreen were shown to exhibit what could be described as synergism between the two components and were shown to exhibit an anti-inflammatory affect which is surprising in light of present knowledge. Without being bound to theory, it is considered that the linseed oil contains one or more active ingredients such as alpha and gamma-linolenic acid which have a primary anti-inflammatory effect. Linseed oil has a very high proportion of alpha and gamma-linolenic acid.

Therefore, as used throughout this specification, the term "linseed oil" also embraces the chemical equivalents thereof and components thereof and thus will include the primary constituents such as alpha and gamma-linolenic acids, or any other constituents shown by experimentation to be active in the relief of inflammation.

Distilled turpentine is an essential oil which is distilled from turpentine, an oily substance derived from

pine cones, which contain several terpenes such as pinene and diapentene. The use of the term "distilled turpentine" herein embraces various turpentine oils such as gum turpentine and wood turpentines as well as the major constituents thereof and the synthetic analogs.

The use of the term "mineral turpentine" includes any of a number of narrow boiling fractions of the petroleum with boiling points in the order of about 200°F to 300°F.

The above mentioned salicylate esters (particulary methyl salicylate) also have a mild analgesic effect on their own and so may enhance the pain relief primarily attributable to linseed oil.

Linseed oil itself is available in different forms, these being primarily cold pressed edible, boiled and pigmented oils, with each being effective in the present invention.

In one form of the invention, the composition includes a propellant for application to the skin as an aerosol spray-on. The choice of propellant will be readily apparent to those skilled in the art.

DESCRIPTION OF PREFERRED EMBODIMENTS

In order that the invention may be more readily understood and put into practical effect, reference will now be made to the following examples.

Example 1

Initial tests on the composition of the present invention were conducted in the following manner.

Four formulations were used: L1, L2, L3 and L4. Theseformulations were as foll ws (all percentages are expressed by volume:

L1:	50%	mineral turpentine
	35%	linseed oil
	10%	methyl salicylate
	5%	eucalyptus oil.
L2:	25%	gum turpentine
	25%	mineral turpentine
	35%	linseed oil
	10%	methyl salicylate
	5%	eucalyptus oil.
L3:	50%	mineral turpentine
	35%	corn oil
	10%	methyl salicylate
	5%	eucalyptus oil.
L4:	50%	corn oil
	35%	linseed oil
	10%	methyl salicylate
	5%	eucalyptus oil.

Five groups, each of four Dark Agouti rats were used. Groups 1 to 4 challenged on day one with Freund's complete adjuvant, composed of 500 micrograms delipidated, heat killed Mycobacterium tuberculosis (human) dispersed in 50 microliters squalane by injection into the tail base. Group five was used as a control and was not subjected to the pretr atment step.

Chronic polyarthritis develops in the rats in all limbs and along the tail after about 12 days.

Treatment with the compositions was begun on day 12 for four days and daily scores of arthritis parameters were taken from the beginning of treatment to day 19. Treatment was by rubbing the limb joints with a 0.5ml dose of the particular composition.

Arthritis (or inflammation) is scored by the mean increase in tail and rear paw pad thicknesses, mean change of weight and mean forepaw thickness increase in an arbitrary index of scale 0 to 6+.

The results were as follows:

TABLE 1

Treatment	Parameters			
	Rear Pads(mm)	Tail(mm)	Front Pads(index)	Change wt(g)
Control	1.59	1.15	5+	-21
L1	-0.79	-0.10	1+	-14
L2	0.86	0	2+	-07
L3	1.37	0.55	5+	-11
L4	1.52	0.10	5+	-12

From the above Table 1, it will be seen that the results for the L1 and L2 formulations were statistically significant and gave significant reduction in inflammation. The L3 and L4 formulations provided no statistically

different results to the controls. This is perhaps surprising in the case of the L4 formulation which contains 35% linseed oil, but this ineffectiveness may be attributable to the low content of the linseed oil, the competitive presence of inert corn oil and the low content of thinner.

The above test is indicative of anti-inflammatory activity rather than any analgesic effect created by the topical application of the composition. The anti-inflammatory effect noted with the combination of linseed oil and mineral turpentine is unexpected and surprising in the light of present knowledge. Moreover, there appears to be a slight reduction in the effect with the use of 25% gum turpentine and 25% mineral turpentine. However, there is still a significant reduction in inflammation and accordingly it is still to be embraced by the present invention.

The preceding treatment protocol was also used in determining the efficacy of the compositions described in the following examples.

Example 2

Further experiments were conducted with 2 component formulations, that is edible linseed oil mixed with ethyl salicylate in varying proportions/isopropyl salicylate/other esters/eucalyptus oil.

The two most active drug preparations known to the inventors that will prevent arthritis expression over the time period routinely used in these liniment assays are Piroxicam dissolved in DMSO and copper-phenylbutazon

dissolved in DMSO-glycerol. They were accordingly compared with linseed oil thinned with either an eucalyptus oil of illdefined composition or with ethyl salicylate. The results given in Table 2 are all the more satisfying inasmuch as the Piroxicam and Cu-phenylbutazone formulations each cause gastric bleeding, even though given topically. By contrast the linseed oil formulations were both effective and non gastro-irritant.

In the following Tables, mean rear paw pad thickness increase is identified under the columns headed by the numerals 1 and 5, mean tail thickness increase identified under the columns headed by the numerals 2 and 6, mean front paw pad thickness increase identified under the columns headed 3 and 7, and mean change of weight identified under the columns headed by the numerals 4 and 8.

TABLE 2

	Days 12-15				Days 16-19			
Treatment	1	2	3	4	5	6	7	8
Control	2.91	0.62	6+	-06	-0.6	0.65	1.3+	-13
ELO-Es 7:3	0.86	-0.25	3+	-08	1.13	0.25	2+	-13
ELO-Eo 7:3	1.06	0.45	1.2+	-06	0.55	-0.20	+	-08
DMSO-G 4:1	2.57	0.65	4+	-10	0	0	1.7+	-03
Piroxicam*	0.65	0	2+	-03	0.40	-0.15	0.7+	-03
Cu-PB **	0.32	0.40	0.7+	-12	0.62	0.25	1.3+	-01

* Piroxicam = 1mg/ml (3mM) in DMSO-Glycerol

** (50mM Cu(II)-200mM Phenylbutazone in DMSO-Glycerol

ELO = Edible Linseed Oil

Es = Ethyl Salicylate

Eo = Eucalyptus Oil

DMSO-G = DMSO Glycerol

Example 3

Table 3 gives the data from one experiment in which the proportions of oil: ethyl salicylate were varied from 9:1 to 6:4. Activity was evident in all 4 mixtures but no one mix was clearly optimal. Replacing the ethyl salicylate with isopropyl salicylate gave a somewhat less pungent (more pleasant) liniment that was certainly active. Thus either the methyl, ethyl or isopropyl salicylates will effectively thin the linseed oil and promote skin penetration for anti-arthritic activity. Two other esters, methyl benzoate and amyl acetate were not adequate for this purpose. The amyl acetate was an excellent thinner (resembling acetone), as far as reducing the viscosity of linseed oil, even though it did not promote the anti-arthritic activity. Perhaps it could be used nonetheless in preparing mobile, relatively non-volatile, oil preparations (e.g. for spray-on) that do have anti-arthritic activity.

TABLE 3

Treatment	Days 12-15				Days 16-19			
	1	2	3	4	5	6	7	8
Control	1.94	1.05	3+	-06	0.41	0.10	1.2+	-02
ELO-Es 9:1	0.60	-0.05	+	+05	0.64	0.15	1.2+	0
ELO-Es 8:2	1.10	-0.55	2+	-07	0.41	0.40	2+	-14
ELO-Es 7:3	1.08	-0.10	2+	-08	0.51	0.20	2+	-06
ELO-Es 6:4	0.89	-0.60	0.8+	-02	0.58	0.20	1.5+	-05
ELO-IS 7:3	0.78	-0.15	1.7+	-08	0.05	0	0.7+	+05
ELO-MB 7:3	1.59	-0.10	2.7+	-06	0.41	0.30	1.3+	-03
ELO-AA 7:3	1.72	+0.30	2.3+	-12	0.05	-0.05	0.3+	-04

IS = Isopropyl Salicylate

MB = Methyl Benzoate

AA = Amyl Acytate

Example 4

Experiments were conducted with 2 - component liniments composed of:

a) esters of unsaturated fatty acids with ethyl salicylate;

b) linseed oils thinned with eucalyptol (also known as cineole).

The results indicated linolenic acid (18:3) to be the

principal active agent for suppressing inflammation in rats with experimental polyarthritis.

Ethyl oleate, methyl linoleate and methyl linolenate were procured as 90% pure. They were mixed with ethyl salicylate (23%) for topical application.

The linoleate (18:2) liniment reduced rear paw swelling (column 1 Table 4) but there was no rebound after cessation of dosing and this group may have included a poor reactor. The linolenate (18:3) liniment was certainly remarkable in preventing increase in inflammation, even suppressing pre-established inflammation in the rear paws and tail. On ceasing treatment, there was a very definite increase in the size of inflamed paws and tail. Both the linoleate (18:2) and linolenate (18:3) liniments caused scaliness of the skin at the site of application. The oleate (18:1) liniment also caused some scaling but this was much less apparent.

Another batch of edible linseed oil was used with and without added pure eucalyptol (10%v/v). The results show (i) that ELO alone is not effective and (ii) that eucalyptol can be added to the list of useful thinners.

TABLE 4

Treatment	Days 12-15				Days 16-19			
	1	2	3	4	5	6	7	8
Control	1.68	0.7	4+	+02	0	-1.5	0	-02
EOl-Es 8:2	1.64	-0.05	+	-06	-0.26	-0.30	+	+02
ML-Es 8:2	1.04	-0.25	1.7+	-14	0.05	-0.50	0.5+	+05
MLL-Es 8:2	-0.14	-0.10	0	-07	0.88	0.30	2.3+	+02
ELO only	1.66	0.30	2+	-03	0.10	-0.35	0.5+	-04
ELO-Eul7:3	0.53	0.35	0.7+	+07	1.19	-0.10	1.3+	-03

EOl= Ethyl Oleate (18:1)

ML = Methyl Linoleate (18:2)

MLL= Methyl Linolenate (18:3)

Eul= Eucalyptol

Example 5

A sample of linseed oil low in linolenate (18:3) was obtained from C.S.I.R.O. and compared with the ELO in admixture with 20% ethyl salicylate (Table 5). This 80% ELO liniment was certainly active. The low-linolenate liniment was less active.

TABLE 5

Treatment	Days 12-15				Days 16-19			
	1	2	3	4	5	6	7	8
Control	1.39	0	4+	-09	0.10	0.05	0.7+	-05
ELO-Es* 8:2	0.55	-0.45	0.5+	-08	1.02	0.15	2+	-06
ELO-Es**8:2	0.96	0.70	2.5+	-03	0.66	-0.15	+	-06

* Linseed Oil contains 1.5% Linolenic Acid (18:3)

** Linseed Oil contains 47% Linolenic Acid (18:3)

Example 6

A number of linolenate oils (see Table 6) were tested in combination with ethyl salicylate, to compare with the linseed oil/ethyl salicylate formulation. The results are shown in Table 7 and Table 8.

TABLE 6.

LINOLENATE (18:3) CONTENT OF SOME OILS

alpha - 18:3 in:		%	Source of data
	- Edible Linseed (Blackmore's)	47	product label *
	- Walnut	10.9	S.I.W.
	- Soybean	6.8	S.I.W.
	- Rapeseed	8.6	S.I.W.
	- Experimental Linseed	1.5	C.S.I.R.O.
gamma - 18:3 in:			
	- Evening Primrose (Efamol)	9	product label *
	- Borage seed	11.2	C.S.I.R.O.

* typical analysis as quoted.

S.I.W. Sheppard et al. Handbook of Lipid Research 1:341.

C.S.I.R.O. Divn. Plant Industry, unpublished data.

Three oils with significant content of alpha-linolenate (which is abundant in linseed oil) showed topical activity when thinned with ethyl salicylate. These were walnut, soybean and rapeseed. Muttonbird oil was tested as a formulation with 20% ethyl salicylate and found inactive.

TABLE 7

Treatment	Days 12-15				Days 16-19			
	1	2	3	4	5	6	7	8
Control	1.32	0.80	2+	-11	0.46	0.05	-	-03
ELO-Es oral	1.04	-0.15	1.5+	-02	0.71	-0.1	0.8+	-23
ELO-Es topic	0.44	-0.20	0.3+	-11	1.01	0.20	1.2+	-07
WO-Es topic	0.71	0	+	-13	0.51	-0.15	0.7+	-08
SO-Es topic	0.70	-0.10	2+	-23	0.56	0.10	+	-05
RO-Es topic	0.88	0.20	+	-17	0.78	0.50	2+	-08
IM-Es topic	0.96	0	3.7+	-23	0.05	-0.40	0	-09
MO-Es topic	1.13	-0.15	1.7+	-17	0.40	0.35	1.3+	-01

Formulations contained oil: Es of 8:2 by volume.

WO = Walnut oil

SO = Soybean oil

RO = Rapeseed oil

IM = Isopropyl Myristate

MO = Muttonbird oil

The low-linolenate experimental linseed oil from CSIRO was tested with 20% ethyl salicylate and found to have minimal topical activity (Table 8).

Two oils containing gamma-linolenate, when tested with ethyl salicylate, were also topically active. These were evening primrose and borage seed oils (Table 8).

TABLE 8.

Treatment		Days 12-15 1	2	3	4	Days 16-19 5	6	7	8
Control		1.65	0.77	3.3+	-11	0.17	0.25	0.7+	-07
BO-Es	4:1	0.90	0.20	1.5+	-14	1.23	0.58	+	-06
EPO-Es	4:1	0.85	-0.45	3.3+	-07	0.64	0.25	1.5+	-05
ELO*-Es	4:1	1.38	0.40	1.8+	-15	0.30	-0.15	0.8+	-06

BO = Borage seed oil

EPO = Evening primrose oil

ELO*= Experimental linseed oil.

In a previous study (unreported) using isopropanol or acetone as thinners, the evening primrose oil showed anti-arthritic activity.

Example 7

The efficacy of Ateol (tea tree oil) as a thinner and synergistic agent for linseed oil is shown in experiments described in Table 9.

TABLE 9

Treatment	Days 12-15				Days 16-19			
	1	2	3	4	5	6	7	8
Control	1.42	-0.35	2.1+	+02	0.41	0.47	0.3+	+02
ELO-A 4:1	0.27	-0.40	0.8+	-04	0.83	0.57	1.9+	+06
CO-A 4:1	1.04	-0.10	1.2+	-02	0.59	0.15	2.5+	+01
ELO only	0.93	-0.20	1.70	-01	0.30	0.58	0.3+	+03

A = Ateol

CO = Corn oil

The invention is further illustrated by reference to the following examples using human subjects but the results are based on a more subjective reaction of the subject to the composition.

Example 8

FORMULATION 1

linseed oil	50% v/v
mineral turpentine	50% v/v

The above agents were mixed together and about 1% v/v eucalyptus oil was added to confer a pleasant smell to the composition.

The composition is massaged into the skin surrounding the affected joint once or twice a day. Complete pain relief was noted for several hours after treatment.

COMPARATIVE FORMULATIONS A-C

The linseed oil in the above composition was replaced by castor oil (A), vegetable oil (B) and olive oil (C). None of the compositions A to C gave any appreciable relief of pain over a period of several days as compared to Formulation 1 in which pain relief was significant. Accompanying relief in pain, there is noted also a substantial reduction in the stiffness of the joint.

Example 9

FORMULATION 2

turpentine oil	25% v/v
mineral turpentine	25% v/v
linseed oil	50% v/v

The above components were mixed to a homogenous mixture and about ten drops of eucalyptus oil per 100ml formulation was added.

COMPARATIVE FORMULATION D

turpentine oil	25% v/v
mineral turpentine	25% v/v
olive oil	50% v/v

The above components were mixed and about ten drops of eucalyptus oil were added per 100ml formulation.

The compositions of Formulation 2 and comparative Formulation D were tested on two different subjects, one of

whose elbow joints were seriously affected by arthritis and one of whose fingers on both hands were seriously affected by arthritis.

The composition of Formulation 2 was rubbed on skin surrounding the joints of one limb and the composition of Formulation D was rubbed on the skin surrounding the joints of the other limb.

Over a period of five days, significant pain relief and amelioration of stiffness in the joints with the composition of Formulation 2 were noted whereas the composition of Formulation D had little significant effect. The subjects were not advised as to the nature of either solution and the solutions were only identified by numbers. Both subjects noted the significant relief afforded by the composition of Formulation 2 as compared to Formulation D.

Example 10

FORMULATION 3

turpentine oil	50% v/v
linseed oil	50% v/v

The above components were mixed and topically applied to an affected joint. Significant relief of pain associated with arthritis was noted over a period of several days with twice daily applications of the composition.

COMPARATIVE FORMULATION E.

The efficacy of the composition of Formulation 3 was compared with pure linseed oil, over a period of several days with twice daily application of the compositions to affect d joints. No appreciable affect was noted with the linseed il alone.

Example 11

FORMULATION 4

	linseed oil	90% v/v
Thinner:	oil of wintergreen	7% v/v
	eucalyptus oil	3% v/v

The above components were mixed and the composition tested by application to an affected joint over a period of several days twice daily. A significant reduction in pain was noted over that period.

Example 12

FORMULATIONS 5 TO 9

NO.	LINSEED OIL	METHYL SALICYLATE	TEA TREE OIL	MINERAL TURP
5)	80% v/v	10% v/v	10% v/v	-
6)	80% v/v	20% v/v	-	-
7)	80% v/v	-	20% v/v	-
8)	70% v/v	5% v/v	20% v/v	5% v/v
9)	75% v/v	5% v/v	20% v/v	-

Each of the above five formulations were mixed separately to a homogeneous mixture and applied to an affected joint. Significant relief of pain associated with arthritis was noted over a period of several days with twice daily applications of each formulation.

Various modificati ns may be made in details of composition constituents and method of application without departing from the scope or ambit of the invention.

CLAIMS

1. A composition for topical application to the skin adjacent a locus of inflammation, said composition comprising an oil, being linseed oil or a substantially equivalent oil thereto, or an effective amount of a component thereof, and a thinner therefor which assists in moving said oil or component through the skin to said locus.

2. The composition of claim 1 wherein the substantially equivalent oil is selected from one or more members of the group comprising walnut oil, soybean oil and rapeseed oil.

3. The composition of claim 1 wherein the substantially equivalent oil is selected from one or more members of the group comprising evening primrose oil and borage seed oil.

4. The composition of claim 1 or claim 2 wherein the component of the said oil is alpha-linolenic acid or a derivative thereof.

5. The composition of claim 1 or claim 3 wherein the component of the said oil is gamma-linolenic acid or a derivative thereof.

6. The composition of any one of claims 1 to 5 wherein the thinner is selected from one or more members of the group comprising mineral or distilled turpentine, methyl salicylate, ethyl salicylate, isopropyl salicylate, cineole, ateol and wintergreen oil.

7. The composition of any one of claims 1 to 6 wherein the said oil is present in the composition at about 80% by volume.

8. The composition of any one of claims 1 to 7 further including an antioxidant.

9. The composition of claim 8 wherein the antioxidant is wheatgerm oil or Vitamin E.

10. The composition of claim 1 wherein the oil is linseed oil present in the composition at about 80% by volume and the thinner is methyl salicylate.

11. The composition of claim 1 wherein the oil is linseed oil present in the composition at about 80% by volume and the thinner comprises 10% by volume methyl salicylate and 10% by volume ateol.

12. The composition of claim 1 wherein the oil is linseed oil present in the composition at about 80% by volume and the thinner is ateol.

13. The composition of any one of claims 10 to 12 including an antioxidant conferring amount of Vitamin E.

14. The composition of any one of claims 1 to 13 further including a propellant for application to the skin as an aerosol spray-on.

15. A method for the relief of inflammation, particularly of the joints, said method comprising topically applying to the skin adjacent a locus of inflammation a composition comprising an oil being linseed oil, or a substantially equivalent oil thereto or an effective amount of a component thereof, dissolved in a thinner therefor, which thinner assists in moving said oil or component th reof through th skin to the locus.

16. The method of claim 15 wherein the composition is defined in any one of claims 2 to 14.

17. A composition for topical application to the skin adjacent a locus of inflammation, said composition being substantially as hereinbefore described with reference to the Examples, excluding those used as comparative examples.

18. A method for the relief of inflammation, particularly of the joints, said method comprising topically applying to the skin adjacent a locus of inflammation a composition being substantially as hereinbefore described with reference to the Examples, excluding those used as comparative examples.

INTERNATIONAL SEARCH REPORT

International Application No. PCT/AU 89/00555

I. CLASSIFICATION OF SUBJECT MATTER (if several classification symbols apply, indicate all) 6

According to International Patent Classification (IPC) or to both National Classification and IPC

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II. FIELDS SEARCHED

Minimum Documentation Searched 7

Classification System	Classification Symbols
IPC	A61K 31/20, A61K 35/78

Documentation Searched other than Minimum Documentation to the Extent that such Documents are Included in the Fields Searched 8

AU : IPC as above; Australian Classification M120

III. DOCUMENTS CONSIDERED TO BE RELEVANT 9

Category*	Citation of Document, 11 with indication, where appropriate, of the relevant passages 12	Relevant to Claim No 13
X	EP,A, 266468 (LABORATOIRES NATURA MEDICA) 11 May 1988 (11.05.88) See entire document.	(1-14,17)
X	Patent Abstracts of Japan, C-375, page 12, JP,A, 61-103826 (KAO CORP) 22 May 1986 (22.05.86)	(1-13,17)
X	AU,A, 88875/82 (OLSEN) 14 April 1983 (14.04.83) See entire document.	(1-7,17)
X	DE,A, 2749492 (BIO-OIL RESEARCH LTD) 11 May 1978 (11.05.78) See page 7 lines 12-20, page 10 lines 2-4, page 12 lines 23-26, claims 1-9.	(1-7,10-12,17)
X	GB,A, 1446431 (WILLIAMS) 18 August 1976 (18.08.76) See page 1 lines 71-90, page 2 lines 15-42, Examples I-III, claims 1,5,6,7,11.	(1-13,17)

(continued)

* Special categories of cited documents: 10

"A" document defining the general state of the art which is not considered to be of particular relevance

"E" earlier document but published on or after the international filing date

"L" document which may throw doubts on priority claim(s) or which is cited to establish the publication date of another citation or other special reason (as specified)

"O" document referring to an oral disclosure, use, exhibition or other means

"P" document published prior to the international filing date but later than the priority date claimed

"T" later document published after the international filing date or priority date and not in conflict with the application but cited to understand the principle or theory underlying the invention

"X" document of particular relevance; the claimed invention cannot be considered novel or cannot be considered to involve an inventive step

"Y" document of particular relevance; the claimed invention cannot be considered to involve an inventive step when the document is combined with one or more other such documents, such combination being obvious to a person skilled in the art.

"&" document member of the same patent family

IV. CERTIFICATION

Date of the Actual Completion of the International Search	Date of Mailing of this International Search Report
9 April 1990 (09.04.90)	17 April 1990
International Searching Authority	Signature of Authorized Officer
Australian Patent Office	JOHN G. HANSON

FURTHER INFORMATION CONTINUED FROM THE SECOND SHEET

X	AU,A, 21913/35 (CLUTTERBUCK) 7 May 1936 (07.05.36) See entire document.	(1-7,17)
Y	US,A, 4444755 (HORROBIN) 24 April 1984 (24.04.84) See column 2 lines 37-56, column 4 lines 11-46, column 6 lines 19-31, claim 1.	(1-13,17)
Y	US,A, 4386072 (HORROBIN) 31 May 1983 (31.05.83) See entire document.	(1-13,17)
Y	'Remington's Pharmaceutical Sciences' ed. A.F. Gennaro, seventeenth edition, published 1985, by Mack Publishing Company (Easton, Pennsylvania) see page 1287.	(1-13,17)
Y	'Martindale, The Extra Pharmacopoeia' ed. J.E.F. Reynolds, twenty-eighth edition, published 1982, by The Pharmaceutical Press (London) see pages 263-264, 678, and 684-685.	(1-13,17)

V. [X] OBSERVATIONS WHERE CERTAIN CLAIMS WERE FOUND UNSEARCHABLE 1

This international search report has not been established in respect of certain claims under Article 17(2)(a) for the following reasons:

1.[X] Claim numbers 15,16,18, because they relate to subject matter not required to be searched by this Authority, namely:

See PCT Rule 39.1(iv)
Methods for treatment of the human or animal body, by means of surgery or therapy as well as diagnostic methods.

2.[ ] Claim numbers , because they relate to parts of the international application that do not comply with the prescribed requirements to such an extent that no meaningful international search can be carried out, specifically:

3.[ ] Claim numbers ..., because they are dependent claims and are not drafted in accordance with the second and third sentences of PCT Rule 6.4 (a):

VI. [ ] OBSERVATIONS WHERE UNITY OF INVENTION IS LACKING 2

This International Searching Authority found multiple inventions in this international application as follows:

1.[ ] As all required additional search fees were timely paid by the applicant, this international search report covers all searchable claims of the international application.

2.[ ] As only some of the required additional search fees were timely paid by the applicant, this international search report covers only those claims of the international application for which fees were paid, specifically claims:

3.[ ] No required additional search fees were timely paid by the applicant. Consequently, this international search report is restricted to the invention first mentioned in the claims; it is covered by claim numbers:

4. [ ] As all searchable claims could be searched without effort justifying an additional fee, the International Searching Authority did not invite payment of any additional fee.

Remark on Protest

[ ] The additional search fees were accompanied by applicant's protest.

[ ] No protest accompanied the payment of additional search fees.

ANNEX TO THE INTERNATIONAL SEARCH REPORT ON
INTERNATIONAL APPLICATION NO. PCT/AU 89/00555

This Annex lists the known "A" publication level patent family members relating to the patent documents cited in the above-mentioned international search report. The Australian Patent Office is in no way liable for these particulars which are merely given for the purpose of information.

Patent Document Cited in Search Report	Patent Family Members		
EP 266468			
JP 61103826			
DE 2749492	GB 1580444		
AU 88875/82			
GB 1446431	FR 2197605		
AU 21913/35			
US 4444755	US 4302447 US 4273763 EP 3407	US 4393049 AU 43551/79 JP 54117035	US 4415554 CA 1117012
US 4386072	CA 1193965	EP 68854	FI 822279

END OF ANNEX

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